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Knowledge Gaps in Oncoplastic Breast Surgery

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Unstructured summary

The aims of this Oncoplastic Breast Consortium (OPBC) initiative were to identify important knowledge gaps in the field of oncoplastic breast-conserving surgery (OPS) and nipple- or skin-sparing mastectomy (NSM/SSM) with immediate reconstruction and to recommend appropriate research strategies to address them. A total of 212 surgeons and 26 patient advocates from 55 countries prioritised the fifteen most important from a list of 38 identified knowledge gaps in two electronic Delphi rounds. An interdisciplinary OPBC panel of 63 stakeholders from 20 countries obtained consensus during an in person meeting to select seven of these fifteen knowledge gaps as research priorities: Firstly, the impact of OPS on quality of life and the optimal type and timing of reconstruction after NSM/SSM with planned radiotherapy should be addressed by prospective cohort studies at an international level. Secondly, the role of adjunctive mesh and the positioning of implants during implant-based breast reconstruction should ideally be investigated by randomised controlled trials of pragmatic design. Thirdly, BREAST-Q is a suitable tool to assess primary outcomes in these studies, but other patient reported outcomes metrics should be systematically evaluated and quality indicators of surgical morbidity further assessed.

Introduction

The emphasis on aesthetic outcomes and quality of life (QoL) after breast cancer treatment motivated surgeons to develop oncoplastic breast surgery, which includes oncoplastic breast-conserving surgery (OPS), as well as nipple-sparing mastectomy (NSM) and skin-sparing mastectomy (SSM) with immediate reconstruction. The first oncoplastic breast surgery techniques were introduced into clinical practice over 25 years ago.¹⁻³ Nevertheless, current evidence is based mainly on single-centre observational studies with small sample sizes and short follow up. Applicability and generalisability of study findings in the field of OPS are further limited by the lack of robust study designs and the complex issue of standardisation of these tailored surgical techniques.⁴ Even though NSM and SSM in conjunction with a wide range of options for immediate reconstruction are considered more standardised procedures, many open questions remain when applying them in clinical practice.⁵ Large single-centre series with extended follow-up, prospective multi-centre studies and randomised controlled trials (RCTs) have only recently been published in this important field.⁶⁻⁸

In the past few years, several organisations have systematically evaluated and specified current areas for improvement in surgical breast cancer research and treatment. The Association of Breast Surgery Gap Analysis Working Group described various key research gaps including the need to assess the effectiveness of oncoplastic and reconstructive surgery.⁹ The gap analysis identified several ongoing controversies that need to be resolved in this clinical field. The Swiss, German and Austrian societies of senology convened a consensus conference that revealed substantial heterogeneity in several aspects of clinical OPS practice.¹⁰ Finally, the global Oncoplastic Breast Consortium (OPBC) has identified major disagreement among experts in many questions that are pertinent to NSM with immediate reconstruction.¹¹

The aims of this consensus process were to identify the most important knowledge gaps in the field of oncoplastic breast surgery based on the integration of all types of clinical evidence including experience drawn from contemporary practice and to propose appropriate and practical scientific strategies to address them.

Methods

List of knowledge gaps

The identification of knowledge gaps was performed according to a pre-specified protocol (pages 2-8, supplementary material), as follows: All knowledge gaps were included that were identified by significant disagreement ($\geq 25\%$) among experts during the first international consensus conference on OPS¹⁰ and the first OPBC consensus conference on NSM¹¹. The seven scientific secretaries were tasked with adding key knowledge gaps in oncoplastic breast surgery practice and research to this list based on their expert opinion. All 424 OPBC members were informed via a newsletter of the upcoming Delphi process and were able to give feedback, as well as report additional knowledge gaps. In order to identify key literature in the field that may indicate whether a knowledge gap had already been well addressed, two scientific secretaries performed a specific PubMed search in January 2019 using search terms related to research needs and nipple- or skin-sparing mastectomy and OPS (search strategy: “inconclusive”[tiab] OR “unknown”[tiab] OR “further research”[tiab] OR “research need”[tiab] OR “gap”[tiab] OR “priority”[tiab] OR “unmet”[tiab]) AND “skin AND mastectomy” OR “nipple AND mastectomy” OR (“mammaplasty”[Mesh]) OR (“oncoplastic” OR “oncoplastic surgery” OR “oncoplastic technique” OR “oncoplastic breast conservation” OR “oncoplastic breast reduction” OR “oncoplastic breast surgery” OR “oncoplastic approaches” OR “oncoplastic techniques”) OR (“therapeutic mammaplasty” OR mammaplasties OR mammoplasty OR mammoplasties) OR (“breast conserving surgery” OR “partial breast reconstruction” OR “conservative breast surgery” OR “Breast Conservation Therapy” OR “oncoplastic approach”[tiab]). The same two scientific secretaries queried clinicaltrials.gov (using search terms “breast cancer” for condition/disease and “nipple-sparing” or “skin-sparing” or “oncoplastic”) to obtain information on ongoing clinical trials indicating that knowledge gaps may be sufficiently addressed in the near future. The scientific secretaries adjusted and finalised the list of knowledge gaps.

Delphi process

The prioritisation of knowledge gaps was performed according to a pre-specified Delphi process (pages 3-4, supplementary material). Two rounds of electronic surveys were sent to all OPBC

members to assess the importance of knowledge gaps with anonymised feedback of results.

Importance was defined as need for knowledge to guide clinical practice and research, as opposed to knowledge of theoretical or purely scientific interest.

A personalized access link for the electronic round-one questionnaire was sent out on 24 April 2019 to all 390 surgeons and 34 patient advocates of the OPBC according to the pre-specified timeline. Soon thereafter, several recipients raised concerns about the comprehensibility of the questionnaire for the patient advocates. Therefore, additional lay term explanations for all questions and a glossary prepared by scientific secretaries and a patient advocate (with 30 years of experience in healthcare communication) were sent to all patient advocates.

Participating members were asked to rank the importance of every knowledge gap on a nine-point Likert scale from one (not important) to nine (extremely important) and to recommend ten of them as OPBC research priorities (pages 9-10, supplementary material). A time frame of 2.5 weeks was permitted for submission of the questionnaire with two reminders sent during that time.

All participants from the first round received a second personalised access link to the electronic round-two questionnaire. First-round non-responders were considered to have declined study participation and were not contacted again for the second round. The round-two questionnaire consisted of the same list of knowledge gaps with aggregated feedback from round one. Feedback included the percentage of participants recommending the topic for inclusion in the OPBC research agenda and the median Likert ranking of each item of round one, shown separately for medical professionals, patient advocates and all participants (page 11, supplementary material). Participants were asked to complete the questionnaire again to review, re-rate and re-prioritise the knowledge gaps in light of the above feedback and their own answers to the first round displayed for each knowledge gap. A period of two weeks was permitted to complete round two with two reminders again being sent.

To take account of the preferences of all participating medical professionals and patient advocates, results from round one were used in the final analysis for those participants who did not take part in round two. The proportion of recommendations for inclusion in the OPBC research agenda and the median Likert rating of each knowledge gap were calculated separately for medical professionals and

patient advocates. The mean of the proportion of recommendations and Likert ratings for the two groups was used for ranking of the knowledge gaps. Ranking was determined first by descending proportion of recommendations and second by descending Likert rating. The top 15 ranked knowledge gaps were selected to be discussed at the OPBC consensus conference as potential research priorities.

Delphi participants

There are currently no guidelines for the numbers of participants required for such a Delphi process. Given the complexity of identifying knowledge gaps in clinical practice and research in the field of oncoplastic surgery, we planned *a priori* to recruit a heterogeneous group of specialized surgeons and patient advocates for the process. Firstly, we pre-specified a minimum number of 85 OPBC surgeons from around the world with diversity in terms of background, career-stage, gender, and geography, representing clinicians who perform oncoplastic surgery in daily practice. Secondly, we planned to recruit a minimum of 15 OPBC patient advocates from different countries. The OPBC reflects a heterogeneous consortium of specialists and patient advocates. A first group of OPBC members consists of national coordinators and panellists who have permanent roles within the OPBC. They were invited to join the OPBC based on their expertise in breast cancer management with a practice primarily dedicated to management of breast cancer.¹¹ A second group of OPBC members consists of breast surgeons from various backgrounds with different levels of experience who decided to join the OPBC by self-registration on the OPBC website.¹² The OPBC patient advocacy group consists of patients who underwent breast cancer surgery with or without partial or whole breast reconstruction and volunteered to support the mission of the OPBC. A questionnaire was sent to all OPBC members during the Delphi process to evaluate their background characteristics.

Consensus conference

The consensus conference panel consisted of 63 special guests, OPBC panellists and OPBC patient advocates from 20 countries (pages 12-15, supplementary material). Special guests were selected based on their expertise in medical oncology, radiation oncology, clinical epidemiology or biostatistics with representation from research support units and surgical trainees. The latter responded to a call for trainees in an OPBC newsletter.

Prior to the conference, the 15 top-rated knowledge gaps identified during the Delphi process were sent to the panel with detailed voting results (exact percentage and mean score). The panel met face to face to agree on the list of research priorities and to discuss the most appropriate study designs. Since many of the knowledge gaps were broad-based topics in the field of OPS and NSM/SSM with immediate reconstruction, more focused research questions were developed in the PICO (Patient problem, Intervention, Comparison, and Outcome) format.¹³ This allowed the evaluation of research tools and/or clinical trial designs to address knowledge gaps most appropriately. The degree of appropriateness was assessed according to the methodological quality of the study design, its feasibility and the expected applicability of results to the respective knowledge gaps. The scientific secretaries prepared a concise strategy proposal incorporating both the research question and trial design to address the 15 most important knowledge gaps. The proposal was sent to the panellists in advance and served as basis for discussion during the meeting (pages 16-33, supplementary material).

After two lectures on selection and prioritisation of knowledge gaps, voting on the top 15 identified during the Delphi process took place to determine which of these should become OPBC research priorities (page 34, supplementary material). Voting was in the format yes, no or abstain. Simple majority was defined by agreement among 51–75% of the panellists and consensus by agreement above 75%. In case of consensus to add a knowledge gap to the agenda, the proposed strategy to address this gap was discussed and adjusted live on screen according to the comments of the panel, followed by voting on the strategy (page 35, supplementary material). In case of majority voting on the knowledge gap or respective scientific strategy, discussion and re-voting was encouraged.

Search strategy and selection criteria The results of the Delphi process and consensus conference were brought into context with published, ongoing or planned studies in the form of this review. Literature searches were developed, peer-reviewed and conducted by two information specialists. Medline (via Ovid), Embase (via Elsevier) and Epistemonikos were searched for RCTs, systematic reviews and meta-analyses using text words and subject headings for terms around breast cancer/mastectomy and breast reconstruction/OPS, and standardized filters for study designs were applied.^{14,15} To identify any planned or ongoing studies, Prospero, ClinicalTrials.gov and the WHO International Clinical Trials Registry

Platform were searched (see pages 36-39, supplementary material for full strategy). In a first screening round performed on abstract level, references were excluded by one author (AS) according to the following criteria: study not involving humans, study not on breast cancer, study on basic research only, study without surgical intervention, study on the antibiotic effect of compounds only, study on drains/sealing/dressing only, study on decision aids for patients, study on cost analysis only. A second screening round was performed independently by two authors (GM and EK) on abstract level and references were further selected according to their relevance in respect of the seven selected research priorities. These references were added with full-text to an EndNote X8 library. Finally, the first author (WPW) generated the final reference list from this EndNote X8 library based on currentness and relevance to the scope of this review. Additional references cited within those publications or retrieved from personal files were selectively included.

Findings

A total of 38 knowledge gaps were identified in the field of oncoplastic surgery (table one). During Delphi round one, knowledge gaps were prioritised by 54% (212/390) of OPBC surgeons and 76% (26/34) of OPBC patient advocates who came from 55 countries (see page 40 of supplementary material for characteristics and pages 41-42 for countries of Delphi participants and pages 43-50 for full results of Delphi process). These figures were well above the pre-specified minimum number of Delphi participants requested in the protocol. During Delphi round two, knowledge gaps were re-prioritised by 80% (170/212) of OPBC surgeons and 77% (20/26) of patient advocates. As pre-specified in the protocol, feedback from round one was used for the 20% (42/212) of professionals and 23% (6/26) of patient advocates who completed round one but did not complete round two.

One question was not ranked among the 15 most important knowledge gaps by medical professionals, but was included due to high ranking by patient advocates. Two questions were not ranked among the 15 most important knowledge gaps by patient advocates, but were included due to high ranking by medical professionals. One of these questions was included in the 15 most important knowledge gaps only by re-prioritisation during round two.

The seven OPBC research priorities selected by consensus during the conference are shown in table 2. The iterative discussion and voting process (page 51, supplementary material) achieved consensus on the appropriate research method to address six of the research priorities and a strong majority for one (table 3). The selected research priorities and proposed study designs are discussed below.

What is the optimal type of reconstruction in the setting of planned adjuvant radiotherapy?

This top-ranked knowledge gap was selected as a research priority by 98% of conference participants and the corresponding research question in the PICO format was readily accepted as well.¹³ However, the most appropriate research strategy was heavily debated. A RCT design, as suggested by the scientific secretaries, was not felt to be feasible and the study design selected was a prospective cohort study with propensity score matching and patient-reported satisfaction with breast, assessed by the BREAST-Q questionnaire at two years, as the primary outcome. This design was endorsed by more than three-quarters (79%) of panellists.

What is the optimal timing of reconstruction in the setting of planned adjuvant radiotherapy?

This knowledge gap was ranked second during the Delphi and was added to the OPBC research agenda with strong consensus at initial voting during the conference. While the corresponding PICO question was also promptly accepted, the discussion on the study design mirrored the previous one. Re-voting achieved consensus on a prospective register to optimally address the first two knowledge gaps.

What are the indications for the use of synthetic versus biological versus no mesh in implant-based breast reconstruction?

This knowledge gap ranked fifth in the Delphi process and was only selected as a research priority by re-voting after discussing the limitations of any particular study design to specifically evaluate indications of one versus another device. The panel agreed to address this knowledge gap with a research question focusing on patient satisfaction with initial use of any type of mesh, as opposed to comparing different types of mesh. It recommended a pragmatic non-inferiority RCT design with the BREAST-Q “satisfaction with breast” scale as a long-term patient reported primary outcome, stratified by breast size and degree of ptosis.

What are the indications for the use of pre- vs sub-pectoral implant-based breast reconstruction?

This was the first knowledge gap to be unanimously accepted as an OPBC research priority and also to achieve a consensus recommendation for the most appropriate research question and trial design at initial voting. The panel recommended a pragmatic superiority RCT to address the question of whether patients undergoing pre-pectoral IBBR are more satisfied than patients undergoing sub-pectoral IBBR.

What is the effect of OPS on quality of life?

The panel added this knowledge gap to the agenda with a prompt consensus recommendation to address it by a prospective multi-centre cohort study with propensity score matching and the BREAST-Q “satisfaction with breast” scale as primary endpoint.

What are the best tools to measure the effect of OPS on quality of life and to allow comparison of trial results?

The panel included this knowledge gap in the OPBC research agenda with direct consensus at initial voting. It recommended a similar method to the one used for the present review, consisting of a Delphi process with development based on a systematic review or even meta-analysis followed by a consensus conference. Both of these components should involve patient advocates.

What are the most accurate quality indicators in OPS?

Despite significant overlap between this and previous knowledge gaps, the panel accepted it as a research priority since aesthetic results and QoL are not the only relevant quality indicators. The panel discussed how the disadvantages of OPS should be monitored, especially since OPS reflects a clear escalation of surgery compared to conventional BCS (see figure one for example of a common OPS procedure). Hence, the morbidity associated with OPS is likely to be increased. The panel recommended the risk of complications to be further evaluated in prospective multi-centre cohort studies before deciding on the most accurate quality indicators in OPS.

Discussion

The present process identified several important knowledge gaps in the field of oncoplastic breast surgery and resulted in recommendations for appropriate research strategies to approach them. The optimal type and timing of reconstruction after NSM/SSM with planned radiotherapy were considered the most important knowledge gaps and correspond to areas of controversy in the literature.

Radiotherapy has a major impact on the risk of complications after immediate implant-based breast reconstruction (IBBR) as well as autologous breast reconstruction.^{16,17} A large prospective multi-centre cohort study compared complications and PROs of irradiated and non-irradiated patients who received reconstruction.¹⁸ Autologous reconstruction, which is often not offered by reconstructive surgeons in this context, was associated with lower risk of complications and higher patient satisfaction compared to IBBR. Other series have confirmed these observations, but major controversy persists concerning the use of immediate autologous reconstruction in this setting.¹⁹⁻²³ Indeed, several large series have shown good outcomes after immediate IBBR in the context of radiotherapy as well, with different timing strategies for two-stage immediate IBBR.^{24,25} The recommended OPBC studies, together with other planned or ongoing prospective observational studies and even RCT's, will help select the optimal type and timing of reconstruction when radiotherapy is planned.²⁶⁻²⁹ Finally, preoperative radiotherapy has gained renewed interest as strategy to reduce the risk of radiation-induced toxicity to the reconstructed breast.³⁰ Several observational studies with long-term follow-up suggest that the concept of radiotherapy followed by mastectomy with or without immediate breast reconstruction is oncologically safe.³¹⁻³³

The present work further identified the role of adjunctive mesh and positioning of implants in relation to the pectoral muscle during IBBR as important knowledge gaps. The availability of acellular dermal matrix (ADM) and synthetic meshes for soft tissue coverage has triggered increased usage of one-stage immediate IBBR and subsequently pre-pectoral approaches.³⁴⁻⁴⁰ To date, all published studies on pre-pectoral IBBR are small and observational, mostly suggesting that it is safe and effective.^{35-37,41-44} Sub-pectoral IBBR, however, remains the most commonly performed breast reconstruction in the US.⁴⁵ Several prospective studies are planned or ongoing to assess the role of adjunctive mesh in

different settings.⁴⁶⁻⁴⁸ Three RCTs comparing pre- versus sub-pectoral approaches for immediate IBBR are registered: a tri-centre trial in Denmark and Norway⁴⁹ and single-centre trials from the Mayo Clinic⁵⁰ and Ottawa Hospital Research Institute.⁵¹ The OPBC recently received major public funding from the Swiss National Science Foundation for OPBC-02 / PREPEC, a large international RCT on pre- versus sub-pectoral IBBR after NSM or SSM.⁵² It will test the hypothesis that pre-pectoral IBBR is associated with improved long-term QoL. The primary endpoint will be patient-reported chest physical well-being measured by the BREAST-Q. The trial will include 372 patients across 21 OPBC sites in seven countries with 24 months of follow-up. Randomisation of the first patient is planned for June 2020. The trial was designed by applying the PRECIS-2 requirements for pragmatism, which is in line with the current panel recommendation.⁵³⁻⁵⁶ The study design allows surgeons much flexibility in the technical aspects of surgical decision-making. This may help avoid some of the safety issues encountered in the BRIOS trial.^{7,8} Although the latter revealed no major differences in patient QoL and satisfaction when comparing one- versus two-stage immediate IBBR, the ADM-assisted one-stage approach was associated with significantly higher odds of complications, re-operation, as well as loss of implant, ADM or both. Despite these high rates of complications being partly explained by poor patient selection and lack of experience with a one-stage technique, its safety in routine surgical practice must be questioned.^{57,58}

Finally, the aforementioned process identified the need to investigate the effectiveness of OPS. The association between objective aesthetic outcomes and PROs is complex. Limited available evidence suggests that OPS has a modest impact on patient satisfaction.⁵⁹ An observational study from Brazil found a significantly higher proportion of excellent results after OPS compared to conventional BCS when measured by software and surgeons. However, there were no differences when assessed by patients.⁶⁰ There are at least ten commonly used PRO metrics in breast surgery, and new tools are currently under development.⁶¹⁻⁶³ Determination of the best assessment tool will facilitate QoL measurements across OPBC centres in future studies, but in the meantime, the panel recommended the BREAST-Q for addressing the above knowledge gaps as this is one of the most widely used and comprehensive PRO instruments. It is rigorously developed, validated, specific to breast surgery and available in several languages.⁶⁴⁻⁶⁶ Despite there being no universally accepted approach for

determining the clinical significance of health-related QoL data, first estimates on minimally important differences for the BREAST-Q scores have now been published and these allow sample size calculations for clinical trials.⁶⁷

Clinical indicators of risk in OPS are likely to focus on factors such as rates of complications and return to the operating room as well as delays to start of adjuvant treatments or return to work. A comprehensive review showed high rates of overall and disease-free survival together with low rates of local recurrence, positive margins and re-excisions after OPS. Thus, conventional oncologic parameters do not seem to be discriminatory as critical quality indicators.⁶⁸ Another large review found a wide range of complications after OPS with largely differing risk based on poorly designed and underpowered studies.⁴ The lack of current standards in OPS hampers clinical research in this field. Even though the knowledge gaps referring to OPS classifications systems were ranked low (27th and 30th) in the present Delphi process, the need for standardisation of OPS in clinical research and practice is widely accepted.^{10,69-72} The specific risks associated with various techniques need to be determined to support the development of quality assurance programmes for OPS.

Conclusion

The 2019 OPBC Delphi process and consensus conference resulted in the following recommendations:

Firstly, the optimal type and timing of reconstruction after NSM/SSM with planned radiotherapy should be addressed by prospective cohort studies at an international level. Secondly, the role of adjunctive mesh and the positioning of implants during IBBR should ideally be investigated by RCTs of pragmatic design. Thirdly, the impact of OPS on quality of life should be investigated. While . BREAST-Q is a suitable tool to assess primary outcomes in these studies, other PRO metrics should be systematically evaluated and quality indicators of surgical morbidity further assessed.

The consensus conference panel recognised significant overlap between the prioritised knowledge gaps. It reinforced an earlier recommendation to implement a prospective register based on a defined set of core variables for oncoplastic procedures at OPBC centres.¹¹ Future observational OPBC studies can be embedded in this register, which will also permit the feasibility of any particular RCT to be promptly assessed by real life data from the study sites.

Contributors

WPW and JH initiated and led the whole process chaired the consensus conference. RS coordinated the Delphi process. JdB, MM, MJVP, SP and AP were scientific secretaries. AS, EK and GM selected the references from the literature search for this review. EK, FS, VD, MR, GM, SDS, RS, LC and IF were members of the staff before and during the conference. MG and LH supported the whole process. EG, ME, FF, RK, FB, RR, VZ, SJ, UKE, SK, JMP, VBR, AF, CH, JH, UK, SK, TK, MK, ECT, ZM, MB, TA, MC, TH, GC, CAGE, OG, SK, BK, LK, MJVP, PG, JdB, TS, HCB, SE, UGB, MH, AG, NH, NH, MK, CK, MP, JS, CR, CT, FZ, VL, BG, GK, HK, AS, JB, TK, SP, TR, LR, RV, LW, MET, MM, VS were panellists. All authors contributed substantially to the design of the work, as well as to the acquisition and analysis of data. All authors helped draft the work, revised it critically for important intellectual content, and read and approved the final version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy of any part of the work are appropriately investigated and resolved.

Declaration of interests

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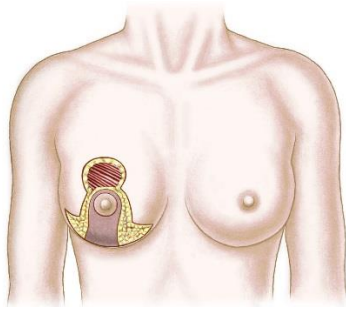
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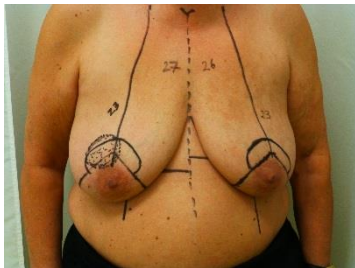
Supplementary Material (uploaded as single PDF file)

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Figure 1: Right oncoplastic reduction mammoplasty with inferior pedicle for supraareolar tumour and left reduction mammoplasty for symmetry



A: Procedure at a glance



B: Patient before surgery with preoperative marking of tumour, landmarks and new position of the nipple



C: Right oncoplastic supraareolar en bloc tumorectomy



D: Bilateral reduction mammoplasty with inferior pedicle



E: Patient one year after surgery

Table 1: Final ranking of knowledge gaps in oncoplastic surgery prioritised during the Delphi process	Recommendation rate*	Likert scale mean rating†
(1) What is the optimal type of reconstruction in the setting of planned adjuvant radiotherapy?	60.9%	7
(2) What is the optimal timing of reconstruction in the setting of planned adjuvant radiotherapy?	57.1%	7
(3) What is the effect of OPS on local recurrence risk?	48.9%	7.5
(4) What is the effect of modern radiotherapy on local recurrence risk after OPS in general and the role of partial irradiation and radiotherapy boost, when larger margins are achieved, in particular?	47.8%	7.5
(5) What are the indications for the use of synthetic versus biological versus no mesh in implant-based breast reconstruction (IBBR)?	47.8%	7
(6) What are the indications for the use of pre- vs sub-pectoral IBBR?	47.7%	7.5
(7) What is the effect of OPS on quality of life?	42.8%	7.5
(8) What is the clinical relevance of breast implant associated-anaplastic large cell lymphoma?	35.2%	7
(9) What are the best tools to measure the effect of OPS on quality of life and to allow comparison of trial results?	34.3%	7
(10) What are the indications for the use of one- vs two-stage IBBR?‡	32.8%	6.75
(11) What are contraindications for nipple preservation?	32.4%	7
(12) What are the most accurate quality indicators in OPS?	29.8%	7
(13) What are the best localisation techniques for non-palpable tumours in OPS?	28.1%	6.5
(14) What are the indications for contralateral prophylactic mastectomy?‡ §	26.9%	7
(15) What are the advantages of OPS compared to conventional breast conserving surgery?¶	24.3%	7
(16) What are the indications for risk-reducing surgery?	23.3%	7
(17) Is NSM/SSM oncologically safe when used for locally advanced breast cancer without the use of neoadjuvant chemotherapy?	22.2%	6
(18) What is the impact of surgical technology on risk of skin flap necrosis (scalpel/scissors vs electrocautery vs Plasma Blade)?	19.8%	6
(19) What are contraindications for skin preservation?	19.5%	7
(20) What is the role of surgical axillary staging in risk-reducing NSM/SSM?	18.9%	6
(21) How can we coordinate training efforts in OPS?***	18.3%	7
(22) What is the best technique for intraoperative skin flap viability assessment to reduce the risk of skin flap necrosis (e.g., indocyanine green fluorescence, thermography)?	17.4%	5.5
(23) What is the optimal site of incision in specific situations (e.g., tumour <1cm from the nipple, upper-inner quadrant tumour in large breast)?	16.9%	6
(24) What is the optimal follow-up (interval, imaging modality) for patients after NSM?	15.9%	7
(25) Does the immediate use of compression bra or compression dressing reduce the risk of skin flap necrosis?	15.8%	5.5
(26) What is the optimal treatment of a positive retroareolar margin?	15.0%	7
(27) How can we optimise current OPS classification systems for use in clinical research?	14.7%	7
(28) What is the role of robotic surgery for NSM?	14.6%	4.75

(29) What is the best treatment of non-infectious skin breakdown after IBBR?	13.8%	6.5
(30) What are the best OPS classification systems for use in clinical practice by professionals and insurance companies?	13.6%	6.5
(31) Should follow-up after risk reducing NSM/SSM be individualised according to the amount of residual breast tissue on imaging?	13.0%	6
(32) What is the optimal timing for contralateral symmetrising procedures?	12.1%	7
(33) What is the role of MRI before NSM?	11.9%	7
(34) What is the optimal follow-up (interval, imaging modality) for patients after SSM?	11.0%	6.75
(35) What is the best treatment for implant-related cellulitis?	10.5%	6
(36) What are the indications for retroareolar frozen section?	8.6%	6
(37) What is the best technique for tissue conditioning to reduce the risk of skin flap necrosis (e.g., nitroglycerine and/or local heat application)?	6.6%	5.5
(38) Should NSM be performed in male patients with breast cancer?	5.2%	5
<p>* Recommendation to discuss this knowledge gap at the consensus conference.</p> <p>† Ranking of importance of every knowledge gap on a 9-point Likert scale from 1 (not important) to 9 (extremely important). Importance was defined as the urgent need of knowledge to guide clinical practice and research.</p> <p>‡ This question was not ranked among the 15 most important knowledge gaps by patient advocates, but was included due to high ranking by medical professionals.</p> <p>§ This question was included in the 15 most important knowledge gaps by reprioritisation during the 2nd Delphi round.</p> <p>¶ This question was not ranked among the 15 most important knowledge gaps by medical professionals, but was included due to high ranking by patient advocates.</p> <p> Dropped out of the 15 most important knowledge gaps due to low ranking by medical professionals.</p> <p>** Dropped out of the 15 most important knowledge gaps due to low ranking by patient advocates.</p> <p>OPS Oncoplastic breast-conserving surgery</p> <p>NSM Nipple-sparing mastectomy</p> <p>SSM Skin-sparing mastectomy</p>		

Table 2: Selection of research priorities from the 15 most important knowledge gaps by the OPBC panel

Knowledge gaps	No. of votes	Yes	No	Abstain	Final recommendation*
Results of final voting					
(1) What is the optimal type of reconstruction in the setting of planned adjuvant radiotherapy?	59	58	1	0	98% (Consensus)
(2) What is the optimal timing of reconstruction in the setting of planned adjuvant radiotherapy?	60	51	6	3	85% (Consensus)
(3) What is the effect of OPS on local recurrence risk?	59	26	31	2	44% (No Consensus)
(4) What is the effect of modern radiotherapy on local recurrence risk after OPS in general and the role of partial irradiation and radiotherapy boost, when larger margins are achieved, in particular?‡	60	26	31	3	43% (No Consensus)
(5) What are the indications for use of synthetic versus biological versus no mesh in implant-based breast reconstruction (IBBR)?	58	50	8	0	86% (Consensus)
(6) What are the indications for use of pre- vs sub-pectoral IBBR?	60	52	3	5	87% (Consensus)
(7) What is the effect of OPS on quality of life?	59	56	3	0	95% (Consensus)
(8) What is the clinical relevance of breast implant associated-anaplastic large cell lymphoma?‡	60	42	17	1	70% (Majority)
(9) What are the best tools to measure the effect of OPS on quality of life and to allow comparison of trial results?	60	51	7	2	85% (Consensus)
(10) What are the indications for the use of one- vs two-stage IBBR?‡	59	40	18	1	68% (Majority)
(11) What are contraindications for nipple preservation?‡	59	39	18	2	66% (Majority)
(12) What are the most accurate quality indicators in OPS?	58	46	12	0	79% (Consensus)
(13) What are the best localisation techniques for non-palpable tumours in OPS?	59	15	41	3	25% (No Consensus)
(14) What are the indications for contralateral prophylactic mastectomy?‡	59	28	31	0	47% (No Consensus)
(15) What are the advantages of OPS compared to conventional breast-conserving surgery?‡	60	41	18	1	68% (Majority)
<p>* Recommendation to include this knowledge gap in the OPBC research agenda based on its importance. Majority was defined by agreement among 51–75% of the panellists and consensus by agreement above 75%. Importance was defined as the urgent need of knowledge to guide clinical practice and research.</p> <p>‡ As pre-specified in the protocol, discussion and re-voting were encouraged in case of initial majority voting (supplementary appendix 1).</p> <p>OPS Oncoplastic breast-conserving surgery</p>					

Table 3: Research priorities with corresponding research question and study design as recommended by the OPBC panel during the consensus conference

Research priorities	Research question in PICO format	Study Design	No. of votes	Yes	No	Abstain	Final voting
What is the optimal type of reconstruction in the setting of planned adjuvant radiotherapy?	P: Are breast cancer patients with planned radiotherapy I: with immediate pre-pectoral implant, radiation, exchange to autologous reconstruction C: compared to immediate autologous reconstruction O: more satisfied with the reconstructed breast at two years after mastectomy	- Prospective cohort study - Propensity score matching - 2 years follow-up - Primary outcome: Satisfaction with breast (BREAST-Q)	58	46	11	1	79% (Consensus)
What is the optimal timing of reconstruction in the setting of planned adjuvant radiotherapy?	P: Are patients with breast cancer who require mastectomy and will need PMRT I: with immediate reconstruction (stratified by technique) C: compared to delayed reconstruction (could have temporary expander) O: more satisfied with breasts?	- Prospective register - 2 years follow-up - Primary outcome: Satisfaction with breast (BREAST-Q)	57	47	7	3	82% (Consensus)
What are the indications for use of synthetic versus biological versus no mesh in implant-based breast reconstruction (IBBR)?	P: Are patients after mastectomy receiving I: immediate pre-pectoral implant reconstruction without ADM or synthetic mesh C: compared to pre-pectoral implant reconstruction with ADM or synthetic mesh O: less satisfied with the reconstructed breast?	- Pragmatic RCT - 1:1 Randomisation - 3 years follow-up - Primary outcome: Satisfaction with breast (BREAST-Q) - Non-inferiority	57	40	12	5	70% (Majority)
What are the indications for the use of pre- vs sub-pectoral IBBR?	P: Are patients after mastectomy receiving I: immediate pre-pectoral implant reconstruction C: compared to immediate sub-pectoral implant reconstruction O: more satisfied with the reconstructed breast?	- Pragmatic RCT - 1:1 Randomisation - 2 years follow-up - Primary outcome: Satisfaction with breast (BREAST-Q) - Superiority	56	47	5	4	84% (Consensus)
What is the effect of OPS on quality of life?	P: Are patients after I: level II* OPS C: compared to standard BCS and mastectomy O: more satisfied with their breasts?	- Prospective multi-centre cohort study - Primary endpoint: Satisfaction with breast (BREAST-Q) - Propensity matching	55	53	2	0	96% (Consensus)
What are the best tools to measure the effect of OPS on quality of life and to allow comparison of trial results?	P: What are the best tools to measure the effect of OPS on quality of life and to allow comparison of trial results?	- Systematic review / meta-analysis - Delphi including patients - Consensus conference with patients	58	44	8	6	76% (Consensus)
(What are the most accurate quality indicators in OPS?)	P: Do patients after I: OPS C: compared to standard BCS or mastectomy O: experience more complications?	- Prospective multi-centre cohort study - Endpoints: complication rate, sick leave, return to work, return to theatre	58	52	6	0	90% (Consensus)

* according to the classification by Clough et al

ADM Acellular Dermal Matrix

BCS Breast-conserving surgery

IBBR Implant-based breast reconstruction

OPS Oncoplastic breast-conserving surgery

PICO Population, Intervention, Comparison, Outcome

PMRT Post-mastectomy radiotherapy

RCT Randomised controlled trial

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